REMARKS

The present invention is directed to pure ondansetron hydrochloride dihydrate. Claims 1-3, 42-50, and newly added claim 51 are pending. In an office action dated May 20, 2005, the Office rejected claims 1-3 and 42-50.

Claims 1-3 and 42-47 have been amended to recite an exo-methylene content of less than about 0.01%. Support for this amendment can be found, *inter alia*, in the specification at page 3, lines 29-31 and at Example 4.

New claim 51 is added to recite ondansetron hydrochloride dihydrate having a purity of at least about 99.9% and an exo-methylene content of less than 0.1%. Support for this amendment can be found, *inter alia*, in the specification at page 2, lines 13-22.

35 U.S.C. § 112 Rejection

Claims 1-3 and 42-50 were rejected under 35 U.S.C. § 112 for failing to comply with the written description requirement. The Office Action states than an exo-methylene content of less than about 0.1% is not described in the specification as filed. Applicants respectfully traverse.

At page 3, lines 29-31, the specification describes an embodiment of pure ondansetron hydrochloride dihydrate "that is substantially free of exo-methylene by-product and has a high purity of at least about 99.0%." To expedite allowance, Applicants have amended the claims to recite an exo-methylene content of less than about 0.01%, a level that is explicitly achieved in Example 4. *See* p. 10, lines 29-32. Because an exo-methylene content of less than about 0.01% is explicitly described in the specification, the rejection of claims 1-3 and 42-50 under 35 U.S.C. § 112 cannot stand and should be withdrawn.

With respect to new claim 51, the specification describes ondansetron hydrochloride dihydrate having a purity of at least about 99.9%. Such pure ondansetron hydrochloride dihydrate has less than 0.1% of impurities including, e.g., the exo-methylene by-product. Page 2, lines 13-22. In this embodiment, the pure ondansetron hydrochloride dihydrate has a purity of 99.9%, therefore it must have less than 0.1% exo-methylene. This embodiment supports new claim 51.

35 U.S.C. § 103 Rejection

Claims 1-3 and 42-50 were rejected under 35 U.S.C. § 103(a) as being obvious in view of Chen, Tyers 1, Coates, Tyers 2, and WO 02/36558 to Lidor-Hadas et al. Applicants respectfully traverse.

To establish *prima facie* obviousness, the prior art references, when combined, must teach or suggest all the claim limitations, there must be some suggestion or motivation to combine the reference teachings, and there must be a reasonable expectation of success. MPEP § 2143.

As described in Applicants' Request for Continued Examination at p. 7, all of the references cited by the Examiner disclose the same inferior process for preparing ondansetron hydrochloride dihydrate. (Applicants' co-pending application WO 02/36558 (U.S. Ser. No. 10/016,752) references the Coates process for preparing the dihydrate. *See* p. 3, lines 12-17.) All of the references teach the solvent system of isopropanol and water, and all of the references teach about 3 equivalents of methyl-imidazole to prepare the ondansetron base starting material. Applicants have repeated Coates to provide exemplary data for this inferior process. *See* Exhibit B, p. 4. Because the prior art does not teach or suggest an exo-methylene content of less than 0.1%, nor less than about 0.01%, the prior art does not teach all of the claim limitations of the present invention.

The Office Action states that less than about 0.1% exo-methylene content reads on the 0.12% exo-methylene content obtained by Coates. Office Action, p. 5. In response, Applicants have amended the claims to recite an exo-methylene content of less than about 0.01% and have added a new claim that recites an exo-methylene content of less than 0.1%. The claims as amended do not read on 0.12%. The prior art exo-methylene content of 0.12% is compared to the low exo-methylene content described in the present invention. *See* Exhibit B, p. 4 and the specification at p. 2, lines 13-22 and Example 4.

The Office Action states that the claimed pure compound is obvious in view of the prior art, which discloses the compound *per se*, but which is silent as to purity. Office Action p. 8. The Office Action cites *Ex parte Hartop* for the proposition that "changing the form, purity, color, or other physical characteristic of an old product without a new use as a result thereof does not render product patentable where the utility remains the same." Office Action p. 9. However, courts have since rejected

this single-factor approach. Utility is not the only factor to consider when determining obviousness. *See In re Cofer*, 354 F.2d 664, 667-68 (C.C.P.A. 1966). Other factors that must be considered include "whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form." *Id.* at 668. In *In re Cofer*, the court held that the pure form of a known compound was not obvious in view of prior art disclosing a less pure form. *Id.* at 831-32.

In the present case, the prior art does not suggest the particular form of the compound, i.e., ondansetron hydrochloride dihydrate having a purity of at least about 99.0% and an exo-methylene content of less than about 0.01%. The Office Action provides no evidence why the claimed product, which exhibits specific and exceptional purity characteristics, would be obvious in view of the prior art, which is silent as to purity. A bald assertion of obviousness is insufficient to maintain the rejection: "Merely stating that compound or composition is obvious, **without adequate factual support, is not sufficient**." *Id.* at 667. (emphasis added). The absence of evidence provided by the Office must be weighed against the experimental results provided by the Applicant. *See* MPEP § 716.01(d). Page 4 of Exhibit B demonstrates that the prior art does not achieve the low levels of exo-methylene as claimed. In comparison, Example 4 of the present application achieves significant improvements in purity. Accordingly, all of the evidence supports the conclusion that the prior art does not teach or suggest the pure product as claimed.

Turning to the second consideration set forth in *In re Cofer*, the prior art does not suggest suitable methods of obtaining the pure compound. As the Examiner correctly points out, the present claims, even those drafted as product-by-process claims, are all directed to the product itself. Office Action pp. 6, 12-13. Applicants have highlighted the unique aspects of the claimed process steps to demonstrate that the prior art does not suggest suitable methods of obtaining the pure compound. Thus, when considering all relevant factors, the pure product as claimed is not obvious in view of the prior art.

To sum, nothing in the prior art enables the skilled artisan to obtain ondansetron hydrochloride dihydrate as pure as that achieved by the present application. Furthermore, nothing in the prior art suggests that such a high level of purity was even possible. Thus, there is no reasonable expectation of success.

Respectfully, the obviousness rejection is based on hindsight gleaned from the present application, which provides, for the first time, pure ondansetron hydrochloride dihydrate and a method for preparing it. Accordingly, the rejection of claims 1-3 and 42-50 under 35 U.S.C. § 103(a) as obvious in view of Chen, Tyers 1, Coates, Tyers 2, and WO 02/36558 cannot stand and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is invited to telephone the undersigned at the number below.

Respectfully Submitted,

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